	Mitoxantrone	
JTE-522	Mitoxantrone,Flour ouracil and Leucovorin	Breast
JTE-522	Vinblastine,Doxoru bicin, Thiotepa, and Fluoxymestrone	Breast
JTE-522	Cyclophosphamide, Methotrexate, Fluorouracil	Breast
JTE-522	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast
JTE-522	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
JTE-522	Fluorouracil, Levamisole	Colon
JTE-522	Leucovorin, Fluorouracil	Colon
JTE-522	Cyclophosphamide, Doxorubicin, Etoposide	Lung
JTE-522	Cyclophosphamide, Doxorubicin, Vincristine	Lung
JTE-522	Etoposide, Carboplatin	Lung
JTE-522	Etoposide, Cisplatin	Lung
JTE-522	Paclitaxel, Carboplatin	Lung
JTE-522	Gemcitabine, Cisplatin	Lung
JTE-522	Paclitaxel, Cisplatin	Lung

Biological Evaluation

COX-2 Inhibitors

1. Lewis Lung Model:

Mice were injected subcutaneously in the left paw (1 x 10^6 tumor cells suspended in 30 % Matrigel) and tumor volume was evaluated using a phlethysmometer twice a week for 30-60 days. Blood was drawn twice during the experiment in a 24 h protocol to assess plasma concentration and total exposure by AUC analysis. The data are expressed as the mean +/- SEM. Student's and Mann-Whitney tests were used to assess differences between means using the InStat software package. Celecoxib given in the diet at doses between 160-3200 ppm retarded the growth of these tumors. The inhibitory effect of celecoxib was dose-dependent and ranged from 48 % to 85 % as compared with the control tumors. Analysis of lung metastasis was done in all the animals by counting metastasis in a stereomicroscope and by histochemical analysis of consecutive lung sections. Celecoxib did not affect lung metastasis at the lower dose of 160 ppm, however surface metastasis was reduced by more than 50 % when given at doses between 480-3200 ppm. In addition, histopathological analysis revealed that celecoxib dose-dependently reduced the size of the metastasic lesions in the lung.

2. HT-29 Model:

Mice were injected subcutaneously in the left paw (1 x 10^6 tumor cells suspended in 30 % Matrigel) and

tumor volume was evaluated using a phlethysmometer twice a week for 30-60 days. Implantation of human colon cancer cells (HT-29) into nude mice produces tumors that will reach 0.6-2 ml between 30-50 days. Blood was drawn twice during the experiment in a 24 h protocol to assess plasma concentration and total exposure by AUC analysis. The data are expressed as the mean +/- SEM. Student's and Mann-Whitney tests were used to assess differences between means using the InStat software package.

A. Mice injected with HT-29 cancer cells were treated with cytoxin i.p at doses of 50 mg/kg on days 5,7 and 9 in the presence or absence of celecoxib in the diet. The efficacy of both agents were determined by measuring tumor volume. Treatment using a celecoxib related COX-2 inhibitor (SC-58236) reduced tumor volume by 89 %. In the same assay, indomethacin given at near the maximum tolerated dose of 2 mg/kg/day in the drinking water inhibited tumor formation by 77%.. Moreover, the COX-2 selective inhibitor completely inhibited the formation of lung metastasis while the non-selective NSAID indomethacin was ineffective. The results from these studies demonstrate that celecoxib administered in the diet to tumor bearing mice can delay the growth of tumors and metastasis when administered as sole therapy. Moreover, a positive benefit is observed when celecoxib is administered in combination with a cytotoxic agent such as cyclophosphamide.

B. In a second assay, mice injected with HT-29 cancer cells were treated with 5-FU on days 12 through 15. Mice injected with HT-29 cancer cells were treated with 5-FU i.p at doses of 50 mg/kg on days 12, 13, 14,